A feeding chamber, an apparatus and a method for production of doses of dry powder, a method for controlling particle segregation in dry powder during filling

TECHNICAL FIELD

The present invention relates to a method and a device for filling a succession of containers with metered doses of finely divided dry powder, the doses intended for inhalation by means of a dry powder inhaler (DPI).

BACKGROUND

Dosing of drugs is carried out in a number of different ways in the medical service today. Within health care there is a growing interest in medical products based on administering drugs by inhalation of dry medicament powder directly to the airways and lungs of a patient. Interest focuses often on dry powder inhalers (DPI) because they offer effective, quick and user-friendly delivery of many substances formulated as dry powder doses for treatment of many different disorders. Because onset is faster and the efficacy of inhaled doses often are much higher than e.g. orally administered capsules or tablets, the inhalation doses need only be a fraction of the medicament powder mass in an oral capsule or tablet. Thus, there is an increasing demand for relatively low mass, inhalable, metered medicament doses of dry powder, which require better filling methods and devices for making small and exact inhalation doses with low relative standard deviation (RSD).

Volumetric filling is by far the most common method of producing dry powder doses of medication drugs. Normally in a first step a quantity of powder is introduced into a receptacle of specified volume by gravitation, often aided by mechanical energy in the form of impaction or vibration, or the receptacle may be filled by suction force. Then in a second step, after stripping of possible surplus powder, the receptacle is moved to an emptying position, where the powder is unloaded from the receptacle by gravitation and/or mechanical means into a container such as a blister or capsule etc. A plurality of receptacles may be arranged in a filling tool, which is adapted to a mechanism bringing a plurality of containers, e.g. blisters or capsules,

in line with corresponding receptacles so that all metered quantities of powder may be unloaded into the respective containers. The filling tool may be integrated into a filling machine such that the receptacles can be filled and emptied in a more or less continuous, cyclic fashion. Examples of prior art may be studied for instance in publications EP 0 319 131 B1, WO 95/21768, US 6,267,155 B1, US 6,581,650 B2, and DE 202 09 156 U1.

Powders for inhalation need to be finely divided or very porous so that the majority by mass of particles in the powder is between 1 and 5 μm in aerodynamic particle size (AD). Powder particles larger than 5 μm tend not to deposit in the lung when inhaled, but to stick in the mouth and upper airways, where they are medicinally wasted and may even cause adverse side effects. However, finely divided powders are rarely free flowing, but are prone to adhere to all surfaces they come in contact with and the small particles tend to aggregate into lumps. This makes the metering of correct doses more difficult, since the bulk density of the powder may vary considerably from dose to dose even if the bulk density is constant when measured on powder quantities several magnitudes larger than the doses. Metering and filling correct quantities into a dose container is therefore more difficult with low dose masses. However, demand for doses from 5 mg down to 0.1 mg is increasing, putting pressure on the industry to improve methods and devices for metering and filling in the manufacturing stage as well as on dry powder inhalers to improve performance in terms of deaggregation and efficacy. Compacting the powder in the metering receptacle to reduce metering errors can be done, but care must be exercised so that agglomeration is not aggravated and to ensure that the agglomerates may still be de-aggregated by the inhaler.

Furthermore, electrostatic forces, friction forces and van der Waal forces acting on particles become stronger than the gravitation force when particle size diminishes. Medication powders are very susceptible to electrostatic

charging during transportation and handling of powders, especially in dry conditions.

There is a need for improvements in methods and devices for precise metering of medicament doses of finely divided powders for inhalation and consistent, reliable filling of doses into suitable containers for use in inhaler devices.

SUMMARY

The present invention discloses a method and a device for precise, repeatable metering and filling of finely divided dry powder into a preformed container, the container and its contained dose being adapted for inhalation by means of a DPI.

In a particular embodiment of the disclosed method, a powder feeding chamber, having a powder inlet and a powder outlet, is used as an important intermediate process step for a selected dry powder medicament in making the powder of known quality available to a metering receptacle. A portion of the powder is transferred by a suction method into a metering receptacle of a filling tool, which presents a high finish, low friction, face in which the receptacle is made. After filling, a resulting load of powder in the receptacle is emptied into a dose container by ejection from the receptacle using air pressure.

The feeding chamber is intermittently replenished, preferably by a gravitational arrangement, from a bulk source of the selected powder, in order to keep the quantity of powder in the chamber preferably constant. The feeding chamber holds powder equivalent to a multitude of receptacle loads. The present method is suitable for many dry powders, even those that are finely divided and therefore normally not easy-flowing. The disclosed method is a low enthalpy method, i.e. the energy supplied to the powder in all the steps of filling and metering is very low compared to prior art filling

methods. In a particular embodiment of the present invention the powder in the feeding chamber is made to collapse and separated from the walls of the chamber by at least one mechanical member, which preferably moves inside the chamber prior to filling a metering receptacle, such that the body of powder in the chamber is e.g. generally disconnected from the chamber walls. This step is preferably performed immediately before a portion of powder is sucked from the chamber outlet into the receptacle, when the receptacle is lined up with the feeding chamber outlet. A very short and low power suction pulse is sufficient to fill the receptacle with a consistent load of powder repetitively.

In a particular embodiment of the present invention, the feeding chamber outlet is in constant, tight contact with the surface of the filling tool such that particles cannot escape from the powder body in the chamber through the outlet. The filling tool is movable relative the chamber outlet, such that the receptacle may be moved out of contact with the chamber outlet and into a position for emptying the load, although contact is maintained all the time between the chamber outlet and the filling tool. Surprisingly, this relative motion helps to restore the homogeneity of the body of powder in the chamber after filling of a receptacle and the shearing forces, although small, between the powder particles and the filling tool surface even out irregularities in the powder stored in the chamber.

The invention offers the following advantages:

Can be used for producing small doses of dry powder at a high precision and accuracy;

Operates according to low enthalpy principle to obtain low particle aggregation;

Has low and controllable particle segregation;

Provides a relatively constant size gradient of particles during steady state conditions;

Can be used for finely divided particles with low free flowing properties.

Other advantages offered by the present invention will be appreciated upon reading of the description below of embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention, together with further objects and advantages thereof, may best be understood by referring to the following detailed description taken together with the accompanying drawings, in which:

FIG. 1 illustrates in a flow diagram the filling method of the present invention;

FIG. 2 illustrates in a cross section a first embodiment giving an overview of a bulk powder source, a feeding chamber and a filling tool;

FIG. 3 illustrates in a cross section a first embodiment of the filling tool comprising a conical metering receptacle;

FIG. 4 illustrates in principle a cross section of an embodiment of the feeding chamber containing a pillar of powder;

FIG. 5 illustrates in principle a cross section of a first embodiment of the filling tool together with the woven filter, the seals, the air nozzle and the feeding chamber and the pillar of powder during filling of the receptacle;

FIG. 6 illustrates in principle a cross section of a first embodiment of the filling tool, the metered load and the feeding chamber in its start and end position after a filling operation in wait for a new filling operation;

FIG. 7 illustrates in principle a cross section of a first embodiment of the filling tool in an emptying position just before the load is ejected from the receptacle into a dose container;

FIG.8 illustrates in principle a cross section of a first embodiment of the filling tool in an emptying position just after the load has been transferred from the receptacle into a container;

FIG. 9 illustrates in principle a cross section of a first embodiment of the filling tool in a cleaning position;

FIG. 10 illustrates in principle a cross section of a second embodiment of a filling tool and feeding chamber arrangement during filling of the receptacle;

FIG. 11 illustrates in principle a cross section of a second embodiment of a filling tool and feeding chamber arrangement when the filling tool has been moved into an emptying position;

FIG. 12 illustrates in principle a cross section of a second embodiment of the filling tool in an emptying position just before the load is ejected from the receptacle into a dose container correctly positioned for receiving a powder load.

FIG. 13 illustrates in a diagram the concentration of small particles, in this case insulin, in a mixture with large particles as a function of position in a feeding chamber.

DESCRIPTION OF THE INVENTION

The present invention discloses methods, a device and an apparatus for exact metering and volumetric filling of dry powder medicament doses into

preformed containers, where the doses and containers are adapted for administration by inhalation using a dry powder inhaler (DPI). The method according to the present invention is illustrated in a flow diagram in Figure 1.

Prior art methods and devices use primarily cylindrical filling tools having a plurality of generally conical metering cavities, receptacles, which are filled with bulk powder from a source holding large amounts of powder. The cylindrical filling tool is then rotated to an emptying position where the filled receptacles are emptied into suitable packages. However, the quality of the powder being filled into the receptacles drifts over time, because the filling procedure affects the quality of the powder involved in the filling process, not least the fine particle fraction of the powder being filled into the receptacles. Energy is therefore supplied to the bulk powder from various sources, depending on manufacturer preference, in order to mix and homogenize the bulk powder and de-agglomerate particle agglomerates, which may form in the bulk of powder.

The present invention is an improvement of the existing prior art in several respects. Prior art methods and devices often use vibration, sieves and other power devices to transport powder and to prevent particles in powder stores to aggregate. Prior art can be summed up as high enthalpy methods. The present invention uses as little energy as possible to move powder from a bulk store to a metering receptacle. The objective is to preferably avoid segregation (see below), or at least to control it, and to avoid particle aggregation by using a low enthalpy filling system.

Fine powders, suitable for inhalation, having aerodynamic diameters (AD) below 5 μm may be produced by micronizing, e.g. by jet milling or spray-drying. Special dry powder formulations may be produced e.g. in spray-drying processes or in production of very porous particles having much bigger geometric diameters than 5 μm, but still AD less than 5 μm. These

fine powders, containing active agents, are rarely easy flowing and moreover it is often necessary to add excipients to e.g. dilute the potency of the resulting drug. A common method of increasing the flowability of the powder is to mix the active fine powder ingredient with a biologically acceptable excipient having larger particles acting as carriers of the smaller, active fine powder particles. This is an ordered mixture.

However, any powder containing a range of particle sizes, whether it is a perfect, ordered mixture or a single dry powder formulation, runs a risk of having small particles segregate from larger ones when the powder is being transported or handled in a filling process. For instance, small particles tend to fall to the bottom of a store by gravitation, especially if the store is excited, so that over time the concentration of small active particles increases near the bottom of a store leading to depletion at the top of the store. A consequence of this is that the fine particle dose of active agent in the metered doses will drift from too much to too little, or vice versa depending on the filling process, during the run of a filling process, although the metered dose mass is reasonably constant over the whole batch. As a result, the inhaled active dosage will vary considerably depending on whether the dose was produced early or late in a batch run. This is not acceptable, of course. Thus, the filling process must actively handle the problem of segregation and keep it under control.

Now, recognizing the problem of segregation, if powder is being dispensed from the bottom of the store in a continuous filling operation and fresh, unaffected bulk powder is being replenished to the top of the store, the concentration of small powder particles near the bottom will be less than that of new powder at the top, once steady state conditions have been reached. In a particular embodiment of the present invention the powder formulation is released in portions, preferably by gravitation or by other suitable means, from a bulk powder source into a first end inlet opening of a

feeding chamber with a capacity for storing a limited amount of powder enough for a limited number of doses to be produced.

Segregation of the powder is thus limited to a relatively small feeding chamber. Steady state conditions are quickly reached in the body, or so called pillar, of powder existing in the feeding chamber as powder is being dispensed through a powder outlet, typically after a single run of the pillar of powder existing in the chamber, provided, of course, that powder is being received in a suitable fashion from the bulk powder source to make up for powder being dispensed from the feeding chamber outlet. Thus, after an initial filling of the feeding chamber, the bulk powder is intermittently fed in relatively small portions to the chamber inlet to compensate for the discrete powder flow from the chamber outlet during dose metering and filling. The feeding chamber is arranged to preserve the quality and properties of the bulk powder, while the powder particles are transported as a slow plug-like, discreet flow from the chamber inlet to the chamber outlet. Contrary to prior art, the present method uses very little power in transporting the powder and the present method avoids adding energy to break up particle agglomerates, simply because agglomerates do not form spontaneously in the feeding chamber. Thus, the properties of the bulk powder are left intact from the feeding chamber inlet to its outlet. However, after an initial start-up period of a limited number of doses having been produced, a steady state condition is reached, characterized by a certain gradient of fine particle depletion being formed in the powder contained in the feeding chamber, going from the inlet to the outlet. After the initial start up period, the concentration of fine particles is always less in the powder close to the outlet, compared to the bulk powder being filled at the inlet of the feeding chamber. The gradient and depletion are kept at acceptable values, because the feeding chamber is intermittently replenished by a portion of bulk powder, whereby the body of powder in the feeding chamber is kept within safe limits. The degree of depletion depends on the powder formulation and the particle size distribution.

Applying the present method of making the bulk powder available to a filling procedure ensures that dose to dose variability in terms of dose mass and fine particle fraction are dramatically improved compared to prior art filling methods. A diagram is shown in Figure 13 illustrating the segregation phenomenon in a filling operation. The example shown is from a mixture of lactose and insulin in an 80/20 relationship, where the insulin powder consists of small particles below 5 μm in diameter and the lactose particles are approximately 10 times larger. The concentration of small insulin particles in the powder is plotted against the position of a sample taken in the feeding chamber. The concentration of small particles drops considerably towards the bottom or outlet end of the feeding chamber.

Preferably, the feeding chamber is cylindrical in shape and the axis vertical for ease of filling and emptying, although other shapes and arrangements will be obvious to a person skilled in the art and such variations are still within the scope of the present invention. The chamber is optionally provided with at least one energizable member, e.g. a scraping, vibrating or flexing member, capable of collapsing the pillar of powder in the feeding chamber, thereby maintaining a plug-like flow of powder through the chamber Furthermore, in a particular embodiment of the present invention, the chamber and at least one scraping member are rotatable in relation to each other, such that the at least one scraping member can move relative the chamber wall, to cover at least a portion of a full revolution, thereby separating powder from the interior wall in the section of the chamber, which is covered by the relative motion. The one or more scraping members work so that the whole inside surface of the chamber is wiped clean of powder before a filling operation is permitted to begin. The scraping action creates a cylindrical pillar of powder, which is generally free from contact with the inside wall of the chamber. Advantageously, the scraping member or members are made slightly shorter than the full chamber length, including an optional outlet piece. In the preferred vertical position of the

chamber, the powder pillar is prevented from falling out of the chamber through a second end outlet opening by a filling tool surface in forcible contact with the outlet end of the chamber. Given an opportunity, the powder pillar is thus free to move along its centre line as a porous pillar of powder, thereby avoiding random segregation of small particles from larger particles in the pillar due to high tap density and ensuing shearing and frictional forces.

A particular embodiment of the feeding chamber has a separate piece constituting the outlet end of the chamber, the outlet piece being movable along the centre line of the chamber. The outlet piece is preferably spring mounted to the chamber, thereby creating the force between the outlet end and the filling tool surface. The outlet piece constitutes a scraper in this way and can be made of a different material from the chamber itself. The material and surface finish may e.g. be selected for minimizing the friction against the filling tool. In a particular embodiment of the invention the filling tool surface is plane and highly finished. Other embodiments of the invention may comprise non-plane filling tool surfaces, such as part cylindrical or part spherical.

The present invention further discloses a filling tool having at least one cavity in a preferably plane surface of high fineness. The cavity forms a receptacle for metering a pre-determined amount of powder. The size and volume of the receptacle determines the amount of load of a selected type of powder that results from the disclosed filling method, but the load is typically in a range from 0.1 mg to 50 mg and preferably in a range from 0.1 mg to 10 mg and more preferably in a range from 0.1 mg to 5 mg. The shape of the receptacle may be adapted to a selected type of receiving dose container, for instance the receptacle may be truncated, conical, spherical, cubical or generally oblong in shape. Further, the receptacle has a first opening in the plane surface of the filling tool and a second, typically smaller opening inside the filling tool. A filter may be applied to the second opening

and an air nozzle may be connected to the other side of the filter to be used in a filling and emptying operation. The filling tool is preferably made of two or more parts, such that each area containing a receptacle constitutes a first part, which is removable from the rest of the filling tool, constituting a second part. Thus, the first part is removed from the second part when the feeding chamber outlet is not in contact with the first part containing a filled receptacle about to be emptied and relieved of its load. After emptying, the first part of the filling tool is restored into the second part of the filling tool. In this way, the outlet of the feeding chamber never loses contact with the filling tool surface of the second part. When removed for emptying, the first part of the filling tool is preferably turned so that the first opening of the receptacle is facing downwards, such that when the air pulse ejects the load, it is helped by gravitation into a selected container.

In another embodiment of the present invention the filling tool is a single item per receptacle. The receptacle may be filled through the first opening and emptied through the second opening. At the filling stage the first opening is uncovered to let powder in, while a second filter is applied to the second opening during the filling operation. The receptacle is filled by suction through the filter when the feeding chamber outlet is in correct position relative the receptacle. At the emptying stage a first filter is applied to the first opening of the receptacle and the second opening is left open by the first filter being removed at this point, such that when a pulse of air pressure is applied to the first opening through the filter, the load in the receptacle is ejected into a selected container.

According to the present invention a filling sequence involves the following steps, illustrated in Figure 1:

I.(Step 2 in Figure 1) A feeding chamber, having an open, outlet end in contact with a filling tool surface, is set in motion relative a filling tool, such that a receptacle of the filling tool is brought in line with the outlet end of the feeding chamber, the diameter of which being bigger

than the first opening of the receptacle. The optional at least one energizable member is energized concurrently with the motion of the chamber, thereby creating a pillar of powder.

II.(Step 3 in Figure 1) When the first opening of the receptacle is lined up with the feeding chamber outlet, a pulse of suction is applied to the second opening of the receptacle, whereby a portion of the powder pillar in the feeding chamber is sucked into the receptacle, filling it completely. Surplus powder, not fitting into the receptacle, remains in the feeding chamber, because the exterior, surface of the filling tool is in forcible contact with the outlet opening of the feeding chamber, leaving no escape for surplus powder out of the feeding chamber. The applied suction moves the whole pillar of powder plug-wise towards the outlet end and helps to even out irregularities and to a degree compact the powder in the feeding chamber, so that the pillar of powder in the chamber is restored. Before the chamber outlet moves outside the receptacle, the pulse of suction is stopped. Optionally the suction is performed when the chamber is momentarily stopped in a position where the receptacle is lined up with the chamber outlet, but typically a pulse of suction is applied while the chamber moves in relation to the filling tool.

III.(Step 4 in Figure 1) The first or only part of the filling tool, carrying the load in the receptacle, is next moved to an emptying position, where the metered load is ejected by a pulse of air pressure directed to the second opening of the receptacle if the intention is to eject the load out through the first opening, or vice versa, such that the load drops into a dose container.

IV. (Step 5, and 6 in Figure 1) If more than one load represents a dose the number of loads dropped into a container must be counted.

V. (Step 7 and 8 in Figure 1) After a dose has been loaded into the container the container is sealed and sent to packaging. A new container is made ready to accept load(s) of powder.

VI. (Step 9 in Figure 1) Optionally the receptacle is cleaned, e.g. by vacuum cleaning, before being restored to a filling position.

VII. (Step 1 in Figure 1) The feeding chamber may now be filled up, if necessary, with powder from the bulk source and a renewed pillar may be formed in the chamber in wait for a new filling operation.

In a particular embodiment of the present invention the feeding chamber rotates in relation to the energizable member(s) or vice versa, while the chamber moves towards the filling tool to bring the chamber outlet in position relative a receptacle, so that the receptacle may be filled with powder from the powder pillar. The chamber outlet is in constant contact with the surface of the filling tool during all relative motions. Thus, the powder pillar at the chamber outlet is subjected to shear forces because of the rotation and motion between the pillar in the chamber and the filling tool surface. The shear and friction forces, though the latter are made as small as possible by careful selection of materials and finishing, help to even out differences in bulk densities throughout the pillar. More porous parts of the powder pillar arising when escaping particles are sucked into the filling tool receptacle, are filled up as the pillar collapses by the weight of the combined particles in the pillar, helped by the suction from the receptacle being filled and the friction forces acting between the powder in the pillar outlet end, the moving and rotating chamber outlet and the plane filling tool surface. The weight or pressure of the pillar onto the filling tool surface is proportional to the bulk density and the height of the pillar, if in an upright position.

The powder in the chamber represents relatively few doses, typically not less than 10 and not more than 100. Having a limited mass of powder in the porous pillar has surprisingly turned out to be a key factor for eliminating uncontrolled segregation of small particles from bigger ones. It is important to keep the mass and height of the powder pillar resonably constant by intermittent topping up from a powder bulk source. It is inevitable, however, that some segregation occurs in the pillar, i.e. a gradient in small particle

concentration will develop going from the first, inlet end to the second, outlet end of the chamber. The degree of gradient will depend on the powder formulation, but once steady state conditions in the filling process are established the gradient will be constant over many cycles of dose filling, far beyond the number of doses in the original body or pillar of powder. It is also most important, when topping up the chamber from a powder bulk source, that the bulk powder is not subjected to the pulse of suction power during e.g. filling of receptacles. The bulk powder should not be subjected to unnecessary sources of energy, because this will increase the risk of segregation within the bulk powder. As little energy as possible should be used to fill up the chamber as necessary, e.g. by arranging the supply of portions of powder to the feeding chamber from the powder bulk source by gravitation only.

Adequate measures should be taken to ensure that no step in the metering and filling procedure can affect the quality of the bulk powder. In a particular embodiment of the present invention the filling apparatus is split into at least three main parts: a bulk source of powder holding an equivalent mass of a large number of doses, a feeding chamber capable of holding a limited quantity of powder corresponding to a limited number of doses and a filling tool comprising at least one metering receptacle for dose forming; where the bulk source discontinuously tops up the feeding chamber with bulk powder and the chamber in turn makes the powder available to the filling tool further down stream. The bulk source of powder is arranged to refill the feeding chamber as often as needed to keep the level of powder therein within specified limits, but only when filling of the at least one receptacle is temporarily inhibited and further such that the powder in the bulk source cannot be affected in any way by the dose metering and filling procedure, which runs autonomously from the bulk source and its refill operation. The feeding chamber, comprising a powder inlet and a powder outlet, is thus given the task of transporting the powder smoothly from the inlet to the outlet on a first-in first-out basis as a coherent plug of powder

using a minimum of energy, preferably gravitation only, in order to make the powder available for a dose metering and filling procedure.

In a further aspect of the present invention the suction energy needed for filling a receptacle is very small, because the structure of the pillar providing the powder is quite porous, but homogeneous. It follows that only a short pulse is needed to attract particles from the pillar into the receptacle, whereby the pillar collapses, but immediately restructures itself from the inlet to the outlet. Typically, the duration of the suction pulse is not less than 0.05 s and not more than 5 s. The pressure used depends on the pressure losses in the pressure system, e.g. losses related to what filters are used, but generally a suction pressure from 0.2 to 20 kPa produces an air flow of not less than 0.1 l/min and not more than 10 l/min.

State of the art as e.g. described in publications US 5,826,633 and DE 103 27 070 A1 differs considerably from the present invention. An important innovation disclosed in the present document is the feeding chamber, which differs from a hopper by not being tapered but cylindrical and optionally having an energizable member, such as a scraping member, preventing powder from sticking to the inside walls of the chamber, whereby it is possible to create a powder body, i.e. a pillar or cylinder of powder, more or less free to move as a plug unit towards the outlet. The problem, common in hoppers, of material sticking and building up - especially when handling finely divided powders having particle sizes below 10 μm - such that powder runs free only in the middle of the hopper, is eliminated in the present invention. In state of the art devices the problem of particle segregation is further aggravated by the use of air suction or mechanical power sources to fill cavities. The more power that is used the more segregation results, especially if the bulk supply of powder is large and also subjected to e.g. suction. Another important aspect of the present invention is the use of a preferably plane filling tool fitting tightly to a chamber outlet, not having a curved surface of a cavity, receptacle, to be filled with powder. In the case of

a vaulted cavity, the connection between the receptacle and the powder supply, such as a hopper, is very difficult to control consistently. Surprisingly, filling and compacting of a load in a plane receptacle becomes much more consistent and easier to control in terms of metered powder mass, compared to a vaulted receptacle.

Surprisingly, the effect of the disclosed filling method is that all particles in the powder pillar, small as well as big ones, move at the same slow pace from the inlet to the outlet of the feeding chamber in a discontinuous motion dictated by the rate of load forming. The method of the present invention and the filling apparatus for carrying out the method imply that the quality of the bulk powder supplied as input material is not becoming deteriorated by the filling process. Particularly, aggregation of particles is not frequent and segregation of small particles from bigger ones is, if not completely eliminated, nevertheless kept under control, leading to steady state conditions during the whole filling operation, regardless of the number of doses produced. Surprisingly, the present invention does not presuppose a more or less free flowing powder, but works equally well for finely divided powders, normally unsuitable for state of the art volume filling methods. Relative standard deviation between delivered fine particle doses is typically less than 3 % and definitely less than 5 % according to USP standards using the present teachings.

In the context of the invention the term "container" is used generically and includes well-known designs such as blisters, capsules as well as bowls and pods, into which a metered quantity of dry powder medicament, a dose, is to be deposited. After filling, the container is closed and sealed, later to be made available in a DPI, which may deliver the dose to a user inhaling through the DPI device. The term "receptacle" is used to describe an open cavity of very exact dimensions and volume made in a plane surface of a filling tool, which may have more than one such cavity in a plurality of plane surfaces, each having at least one receptacle.

From inside the filling tool access can be gained to the preferably smaller opening of the cavity or cavities, each constituting a receptacle, to allow fitting of filters and air supply nozzles, which will be described later.

Embodiments of a device according to the present invention is illustrated in Figures 2 – 12, where like elements are given like numbers in the illustrations.

Figure 2 illustrates in an overview the at least three main parts of a filling equipment comprising a bulk powder source **401**, a feeding chamber **134** and a filling tool **101** and **102**. The bulk powder source contains bulk powder **400**, and an arrangement **410** for releasing a portion of bulk powder when required to top up the pillar of powder **200** in the feeding chamber **134**. The filling tool **101** contains a metering receptacle **110**.

Figure 3 illustrates a filling tool **101** having a plane top surface **103**. The shape and size of a receptacle **110** may vary depending on the size and mass of the powder load to be metered. The conical shape may be circular, rectangular or elliptical, the wideness and depth, i.e. the volume, is adapted to the intended load and the dose container type. Also illustrated are the filter **121**, the seals **122**, the optional stabilizing wire netting or sintered filters **123** and the air connection nozzle **124**.

Figure 4 illustrates in a sectional, principal drawing of an embodiment of a feeding chamber **134** having an inlet opening **132**, an outlet opening **133** and an inner tube **131**. The chamber is further provided with at least one mechanical member **135**. Also illustrated is the movable outlet piece **137** and the expansion spring **136** forcing the outlet piece to contact the plane surface of the filling tool.

Figure 5 illustrates a sectional, stylized, principal drawing of the operational filling tool first part **101** comprising the receptacle fitted to a second filling tool part **102**. The receptacle **110** is illustrated as being filled by powder **201** from the powder pillar **200** in the feeding chamber, which is lined up with the receptacle. The highly finished, plane surfaces **103** of the filling tool parts **101** and **102** are flush with each other. A pulse of air suction **125** is applied to suck powder into the receptacle.

Figure 6 illustrates a sectional, stylized, principal, drawing of a load **202** in the receptacle, which has been scraped flush with the filling tool surface **103** by the outlet piece **137** when the chamber **134** moves relative the filling tool **101**, **102**. The chamber is illustrated when parked in a start and end position after a filling operation. Optionally, a small suction **125** is applied to the air nozzle **124** to keep the load intact while it is transferred to an emptying position.

Figure 7 illustrates a sectional, stylized, principal, drawing of the filling tool **101** removed from the tool **102** and arranged in an emptying position, where the load **202** may be ejected from the receptacle by a pulse of air pressure **126** directed to air nozzle **124**. Container **211** is in position to receive the load.

Figure 8 illustrates a sectional, stylized, principal, drawing of a load **202** deposited into a container **211**. The receptacle **110** is now empty.

Figure 9 illustrates a sectional, stylized, principal, drawing of the filling tool **101** and receptacle **110** in a cleaning position before being returned to filling tool **102**. Cleaning is illustrated as being performed by vacuum cleaning **301** and suction **302** as an example. Other methods are obvious to a person skilled in the art.

Figure 10 illustrates a sectional, stylized, principal, drawing of a second embodiment of a filling tool **101**, comprising a single part only. In this case two similar air nozzles **124** and **127**, comprising similar filters **121** and **128** respectively and including similar seals and optional supportive aids (not illustrated in detail), are used for filling and emptying, respectively. The tool is illustrated in the filling position, similar to Figure 5. However, the receptacle has identical openings, such that the load can be filled through the first opening and easily emptied through the second opening.

Figure 11 illustrates a sectional, stylized, principal, drawing of the second embodiment of a filling tool **101**, now moved together with nozzle **124** into an emptying position, lined up with air nozzle **127**. A small air suction **125** is applied to nozzle **127** in order to keep the load **202** in the receptacle so that nozzle **124** can be moved back into a filling position once again. The load has been scraped flush with the filling tool surface **103** by the outlet piece **137** when the chamber **134** has moved relative the filling tool **101**. The chamber is illustrated when parked in a start and end position after a filling operation.

Figure 12 illustrates a sectional, stylized, principal, drawing of the second embodiment of a filling tool **101**, in an emptying position, lined up with air nozzle **127** and a dose container **103** correctly positioned and ready to receive the load **202**, being ejected by an applied air pressure pulse **126** to nozzle **127**. Nozzle **124** is shown moving back into its filling position.

According to the present invention, a second opening of the receptacle is connected to an air nozzle, which in turn is connected to a supply of vacuum and compressed air e.g. through fast acting on-off valves. The preferably woven filter between the nozzle and the second opening of the receptacle stops powder from entering the nozzle. After completing filling of at least one receptacle of the filling tool, the tool is moved to an unloading position and, optionally, during the motion the load is prevented from falling out of the

receptacle by a small suction being applied. When in emptying position, the optional suction is terminated and a pulse of compressed air is applied to the second opening of the receptacle, where the air exerts a force on the powder load. The load is thereby ejected from the receptacle and dropped into a selected container, provided it is in correct position. The degree of compaction in the load is preferably adjusted by balancing the pulse of suction during filling, such that the load may be ejected from the receptacle as a non-dusting, porous body of joined particles, not as a cloud of powder. Afterwards, the filling tool is optionally moved to a cleaning position where receptacles are cleaned from any retained particles by air suction. The filling tool is then prepared for a new filling operation.

A filter is necessary when using air to attract or repel powder into or out of a receptacle. A well-balanced suction force applied to a receptacle will attract powder from the feeding chamber and fill up the receptacle, such that the powder is compacted to a certain degree in the receptacle acting as a metering chamber. The filter at the second opening of the receptacle stops powder from being sucked into the air system and thereby becoming lost in the filling process. The filter is also necessary when air pressure is used to push the load out of the receptacle during the unloading operation, because it will stop any foreign particles in the air supply system from contaminating the powder in the load. The filter should not be made of felt, because felt material may give off fibers, which may contaminate the powder load. Felt filters are usually rather thick and the fibers in the felt are not held in place by design; the felt is just a compressed collection of fibers, randomly arranged and held together by a bonding agent and a more or less loose fabric. In use, the felt will let go of fibers, which may mix into the powder and follow the powder load into the container. The present invention preferably uses a woven, pre-stretched, surface-treated thin filter as manufactured by e.g. W. L. Gore & Associates, Inc. of Newark Delaware, which by design cannot lose fibers to air passing through. A further advantage of the invention is that the filter is so thin that it is easily sealed

to the air connection end of the metering receptacle. Instead of common prior art practice of squeezing the felt filter tight to the receptacle by mechanical high force deforming the thick felt, the stretched woven filter is held in place by an elastic seal, which seals the filter to the bottom end of the receptacle, preferably using an arrangement comprising a resilient, moderate spring force acting on the air nozzle on the other side of the seal, whereby the contact pressure is kept constant, thus maintaining a tight connection between the air nozzle and the air connection end of the receptacle. The seals should be non-fibrous and may be made of e.g. PTFE, PFA, EPDM, Neoprene or Nitril and similar, medically approved materials. A further advantage of the invention is that the woven filter requires much less differential pressure across it compared to a felt filter for a given flow and particle filtration, i.e. less energy is needed, which simplifies control of the filling and unloading operations.

Proper metering of the powder quantity in the receptacle is difficult but important and consistency between loads coming out of the same receptacle is of course also important and so is consistency between loads from different receptacles involved in the filling process, if there are more than one. A prior art felt filter is easily deformed when it is squeezed tight to the air connection end of a receptacle, e.g. by pushing an air nozzle with considerable force into the felt. The felt will bulge inwards and intrude into the bottom of the metering receptacle, thus reducing the actual volume in the receptacle, which in turn reduces the powder load sucked into the receptacle in the filling step and results in lower powder mass in the load to be transferred to a receiving container. The present invention solves this problem by using a pre-stretched, woven filter, which flexes very little by the moderate forces resulting from air suction during filling and air pressure during emptying. However, the volume of the receptacle increases slightly during filling, because the filter bulges slightly in the direction of the suction. In a particular embodiment of the present invention a supporting wire netting or sintered filter is used to support the woven filter on one or

both sides. Preferably, the supportive netting or sintered filter is applied only on the suction side of the woven filter to stop the bulging effect during filling, thereby maintaining the nominal receptacle volume. Bulging in the opposite direction, however, is an advantage in the ejecting mode, helping the air pressure to push out the load from the receptacle. It is also possible to integrate the woven filter with a suitable sintered filter as a single filter product, rather than using separate items. Surprisingly, an optimized use of filters as disclosed results not only in a reduced relative standard deviation (RSD) between subsequent loads from the same receptacle but also less RSD between loads from different receptacles.

Surprisingly, it has also been found that the retention of powder in the metering receptacle after unloading is less when using the woven filter compared to the felt ditto. The reason for this is that because the felt filter of prior art becomes quite deformed and quite dense around the edges, where it is kept tight to the air connection end, pressurized air may only pass through with great difficulty near the inner wall of the receptacle during the ejection of the load. This phenomenon leads to a substantially reduced air stream near the receptacle inner wall with insufficient turbulence to clean out all of the powder adhering to the wall. However, even when the woven filter is used instead of the felt filter the taper angles of the receptacle walls should not be too wide, otherwise there is a risk that powder retention on the inner walls of the receptacle increases due to insufficient air turbulence near the wall. Preferably, the taper angles between the walls and the centerline of the receptacle are in a range 3 – 30 degrees, more preferably in a range 6 – 20 degrees and most preferably in a range 9 - 15 degrees.

Reducing powder retention on all surfaces that may come in contact with powder is a further aspect of the present invention. The material of the feeding chamber, the filling tool and other parts coming into contact with the powder, is carefully selected to present extreme stability of form, good machining properties, good resistance to abrasion, high surface finish with

low friction properties, if necessary achieved by coating. Suitable materials for the filling tool etc. include for instance vacuum-arc-remelted (VAR) stainless steel, metals, alloys, peek and glass. Suitable coating materials may be selected from thermoplastic materials, such as PTFE, PE, parylene and similar. The tool surfaces in contact with powder, e.g. the metering receptacles, should be polished or coated to a fineness modulus of less than R_a=0.25 μm, and preferably less than R_a=0.1 μm and the resulting surface should present as low dynamic friction coefficient as possible. A preferred embodiment of the filling tool uses a machined stainless steel body, which is ground in several steps, further polished and then optionally electro-polished, which results in a fineness of less than R_a=0.1 μm. The filling tool and other parts may then be metallurgically coated by vapor deposition of e.g. chromium nitride, coal/chrome-combination or graphitic coating. This will ensure a durable surface with very low friction, making it difficult for powder particles to stick to surfaces. Naturally, consideration must be paid to the type of medicament powder and powder formulation in deciding what materials to use and the appropriate grinding and polishing steps and type of coating, if needed.

Electrostatics is often a problem in the handling of dry powders, especially finely divided powders. Fine particles are easily triboelectrically charged when transported, not only by contact with objects of the transportation system but also by flowing air. The problem is aggravated by the necessity of handling the powder in a dry atmosphere, typically below 20 % relative humidity, in order not to affect the quality and properties of the powder. The powder particles may be electrically discharged by applying static elimination devices, e.g. from NRD LLC, Grand Island, New York, where needed to keep static charging of the powder, the filling tool and associated equipment to a minimum throughout the filling procedure. By doing so loss of particles due to particle-sticking and other interference from statics with the filling process are kept to a minimum. When an applied air pressure pulse unloads the powder load from the metering receptacle, the powder

particles must pass an existing air gap before reaching a receiving container. By triboelectric charging, particles aquire a positive or negative charge to a higher or lesser extent. This electric charge makes them disposed by the influence of stray electric fields, existing in the air gap, to deflect in other directions than the expected inertial and gravitational track and thus settle onto other surface areas than the expected target area of the receiving container. To reduce spillage of this sort the present invention discloses the addition of a source of neutralizing charges, e.g. an ion source, to be positioned near the air gap between the tool incorporating metering receptacle(s) and the container(s). Electrically charged particles will then very quickly be neutralized by charges from the source and the loss of particles in transfer from receptacle to container due to electrostatics will be reduced.

The present invention relates to consistent filling of dry powder doses of medicament into containers destined for insertion into a DPI, where the pre-metered doses are in a range 100 μg - 50 mg and preferably in a range 100 μg - 10 mg and most preferably in a range 100 μg - 5 mg and presenting an RSD of 5 % or less. A metered dose in a container may comprise more than one load, but this is by exception and not the normal procedure, because it would take longer time to fill a container with a dose.

What has been said in the foregoing is by example only and many variations to the disclosed embodiments may be obvious to a person of ordinary skill in the art, without departing from the spirit and scope of the invention as defined in the appended claims.